Preoperative Intranasal Mupirocin for Reduction of Surgical Site Infections in Patients Undergoing Non-Cardiac and Non-Orthopedic Procedures: Systematic Review of the Biomedical Literature

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TABLE OF CONTENTS

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Abstract

Background

Surgical site infections continue to be one of the leading causes of nosocomial infections leading to increased patient morbidity and mortality, length of hospital stays and healthcare expenditure. Amongst the many pathogens, Staphylococcus aureus is a leading cause and many efforts have and continue to be made to reduce their incidence. One such intervention is the use of intranasal mupirocin in the preoperative setting to reduce nasal carriage of S. aureus. Recent studies suggest there seems to be a benefit to using mupirocin in this manner to reduce surgical site infections in cardiac and orthopedic surgical populations. This systematic review will address the question of whether such an intervention will reduce surgical site infections in non-cardiac and non-orthopedic surgical populations.

Methods

I searched MEDLINE and Embase databases until 05/2015 in order to identify prospective randomized controlled trials addressing the use of mupirocin in reducing surgical site infections which yielded 162 search results. The studies were selected based on pre-specified criteria. Included studies were prospective randomized controlled trials comparing intranasal mupirocin or intranasal mupirocin and topical chlorhexidine to either standard treatment or placebo. The primary outcome I was interested in was the incidence of surgical site infections. Other outcomes included incidence of *Staphylococcus aureus* specific surgical site infections, narrative or numerical reports on harms, patient compliance, resistance to mupirocin, and mortality rates. I only chose studies that followed patients for a minimum of 30 days postoperatively. I performed duplicate exclusions, title, and abstract and full text review in order to include 4 studies out of the 162 initial search results. Subsequently, I critically appraised each included study in order to perform a risk of bias assessment. I then abstracted study

characteristics, patient characteristics, and outcomes using a standardized data abstraction table. Lastly, I synthesized the abstracted data as part of my qualitative analysis.

Results

There were no reports of statistically significant reductions in either overall surgical site infections or *S. aureus* specific surgical site infections in the four studies included in this systematic review. Reports of resistance to mupirocin were only included in one study. Data on adverse reactions were reported in three of the four included studies and mostly consisted of narrative reports stating that the treatment regimen was well tolerated. Numerical data on incidence of adverse reactions provided in one study were similar in both the treatment and control arms. No life threatening adverse reactions were reported in the included studies. Only one of the four studies provided numerical data on patient compliance whereas the other included studies only provided cursory information on compliance.

Conclusions

Given that there were no statistically significant reductions in surgical site infections or S. aureus specific surgical site infections in the included studies that used mupirocin alone or a combination of both mupirocin and chlorhexidine compared to placebo or standard treatment I do not have sufficient evidence to recommend preoperative prophylaxis in non-cardiac and non-orthopedic surgical populations. However, given that the included studies have limited internal and/or external validity and because the same intervention has been shown to be potentially beneficial in cardiac and orthopedic surgical populations I also don’t have evidence to recommend against it. No conclusions can be drawn regarding resistance or patient compliance as only one study reported on these outcomes. Given the limited number of studies addressing this question in non-orthopedic and non-surgical patients there needs to be additional

randomized controlled trials that are sufficiently powered in these patient populations before definitive conclusions can be drawn.

Background

Surgical site infections continue to be one of the most common healthcare associated infections (HAIs) and lead to increased length of hospital stay and mortality. According to a report by the National Healthcare Safety Network, between January 1, 2006 and December 31, 2008 a total of 849,659 surgical procedures were reported to be done at 847 hospitals in 43 states in the United States. Among these, there were 16,147 primary incisional SSIs (1.90%).[1]

In order to get a better estimate of the national burden of HAIs a study published by the Centers for Disease Control and Prevention (CDC) in the New England Journal of Medicine evaluated prevalence of HAI across 183 hospitals in 10 states in 2011. Of the 11,282 patients evaluated there were 504 total HAIs of which 110 were SSIs. SSIs at 21.8% (18.4-25.6) were ranked number 1, tied with pneumonia also at 21.8% (18.4-25.6) as a cause of HAIs. Amongst causative organisms for surgical site infections that were detected S. aureus came in at number 1 at 18 cases (16.4%), followed by Enterococcus species at 16 case (14.5%).[2]

According to this study that utilized the Healthcare Cost and Utilization Projection National Inpatient Sample (HCUP NIS) that documented 723,490 surgical hospitalizations and 6891 SSIs there were 406,730 additional hospital days and additional hospital costs exceeding 700 million US dollars. Moreover, there were 91,613 additional readmissions for SSI treatments that accounted for another 521,933 days of care costing nearly 700 million US dollars. SSIs on average extend the length of stay by 9.7 days and increasing the cost of by 20,842 per admission.

The following are their reported incidences of SSIs in various surgical categories (Table 1). Also given below are the average length of stay (days) and cost per stay (US dollars) (Figure 1 and Figure 2).

Surgical Sub-specialty	No. of discharges	No. with SSI	Percent with SSI	95% CI
Neurologic	65066	206	0.32	0.27-0.36
Cardiovascular	62347	734	1.18	1.09-1.27
Colorectal	86782	3565	4.11	3.98-4.24
Breast	31863	63	0.20	015-0.25
GI	156258	2032	1.30	1.24-1.36
Orthopedic	52133	132	0.25	0.21-0.30
OB/GYN	269041	159	0.06	0.05-0.07

Table 1: Incidence of SSIs in various surgical specialties.

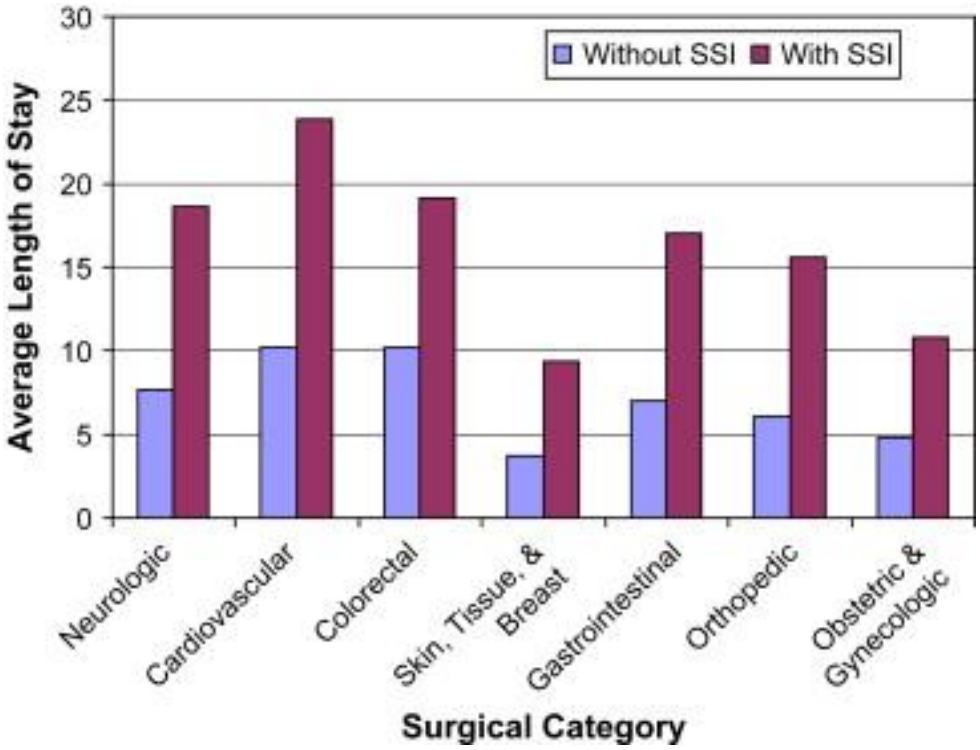

Figure 1: *Average length of stay (days)among patients with and without SSIs in various surgical specialties.*

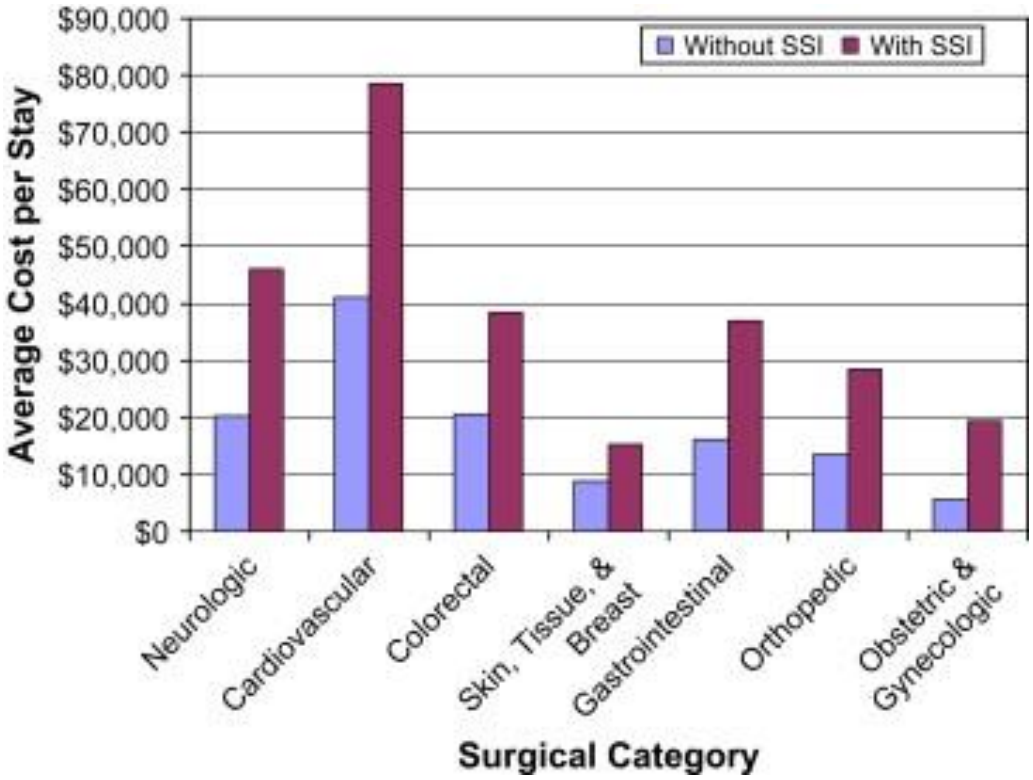

Figure 2: *Average cost per stay (US dollars) among patients with and without SSIs in various surgical specialties.*

However, there exists significant variability in the incidence of SSIs as reported in the published literature (Table 2). Regardless of the variability in incidences found in the literature the consensus remains that SSIs are a preventable cause of burden and suffering for both the patient and the healthcare system.

Surgical Sub-specialty	Range of Incidences
Neurologic	0.5-29%
Cardiovascular	0.8-4.7%
Colorectal	2.6-15%
Breast	0.4-16.3%
GI	1.3-15.5%
Orthopedic	0.6-1.4%
OB/GYN	1.6-9.6%

Table 2: *Range of incidences of SSIs in various surgical specialties found in the biomedical literature.*

The CDC classification of SSIs is given in Figure 3 below.

SSIs	*Incisional*	Superficial	Only skin and subcutaneous tissue
		Deep	Deep soft tissues such as muscle and fascial layers
	Organ/Space		Any part of the anatomy other than the incsions that was opened or manipulated during the operative procedure.

Figure 3: *CDC definition of Surgical Site Infections*

There are several risk factors for surgical site infections that can be classified into the preoperative, perioperative and postoperative categories.

Preoperative	Perioperative	Postoperative	Other
• Diabetes mellitus control • Obesity • Tobacco use • Use of immunosuppressants • Length of preoperative hospitalization	• Wound class • Length of surgery • Shaving of hair • Hypoxia • Hypothermia • Traffic	• Hypoxia • Hypothermia • Diabetes mellitus control • Wound care • Blood transfusions	Age

The development of a surgical site infection is a complex interplay between microbial, patient and surgical characteristics. The contamination could occur endogenously or exogenously. The greatest likelihood of contamination and thereby risk of infection occurs from incision to wound closure which has led to endogenous flora from or near the site of incision being the leading cause of SSIs. Exogenous sources of contamination include flora from

colonized or infected surgical personnel, the operating theater and surgical instruments. These are often much less frequent than an endogenous source of contamination. In the setting of contamination the burden of pathogen inoculated intraoperatively determines the risk of the patient eventually developing an SSI. Given standard antimicrobial prophylaxis an inoculum of greater than 105 microorganism is considered necessary to develop an SSI. However, this number can be markedly reduced should a foreign body be placed as part of the operation.[3]

Staphylococcus aureus, especially methicillin resistant strains of S. aureus have long been source of concern due to its increasing role in surgical site infections. It has been reported that S. aureus strains survive in the nares. The strains found in the nares may vary amongst patients and even within the same patient across their lifespan. Some patients can be intermittent carriers, and others can be non-carriers although the latter group is a minority. Carriage of S. aureus has been shown to be positively correlated with an increased incidence in surgical site infections. The nasal strains have been isolated from patients developing surgical site infections.[3]

Although efforts were made to reduce nasal carriage through antimicrobial prophylaxis as far back as the 1950s, the efficacy of the agents used were inadequate until the use of mupirocin for this purpose in the 1980s.[4] Mupirocin, also known as pseudomonic acid or as BACTROBAN (trade name), was initially identified in 1887 when Garre et al. reported the antagonistic effects of *Pseudomonas fluorescens*. Subsequently, in 1971, Fuller at al. isolated the compound for the first time and reported that it had a wide anti-bacterial spectrum against gram positive and negative bacteria, showed low toxicity and that it was bacteriostatic against S. aureus and E. coli.[5] As the name “pseudomonic acid” could lead to the assumption that the compound was an antimicrobial against Pseudomonas species the now generic name of mupirocin was adopted.[6]

Mupirocin is available as a cream for external use, and in separate ointment formulations for intranasal and external use. Intranasal mupirocin calcium ointment (BACTROBAN) is available in single use 1 gram tubes. The safety and effectiveness of mupirocin calcium use for greater than 5 days have not been established. Also, the use of intranasal mupirocin calcium in children under 12 years of age has not been established.

Contraindications to its use include known hypersensitivity to mupirocin or any other contents of the nasal ointment. Systemic allergic reactions have been reported in patients. Chemically BACTROBAN consists of a calcium salt of mupirocin. The nasal ointment is white to off-white in color and contains 2.15% w/w mupirocin calcium which is equivalent to 2% mupirocin acid. No evidence of systemic absorption of mupirocin has been demonstrated following single or repeated intranasal administrations of 0.2 grams of BACTROBAN nasal ointment 3 times dual for 3 to 5 days in healthy adult male subjects.[7]

After intravenous administration of mupirocin it is metabolized into monic acid an inactive metabolite. The half-life for the former is 20 to 40 minutes and for the latter is 30 to 80 minutes. Monic acid, the inactive metabolite, is predominantly excreted renally. Note that the pharmacokinetics of mupirocin have not been studied in individuals with renal insufficiency.[7]

The antibiotic works as a protein synthesis inhibitor by reversibly binding to bacterial isolecucyltransfer-RNA synthetase. It is highly protein bound (/>97%) and is bactericidal at the concentrations achieved by topical intranasal administration. However, the effect of nasal secretions on the minimum inhibitor concentrations of intranasally applied mupirocin as not been determined.[7]

As someone interested in pursuing a career in general surgery I had been in search of a topic within surgery that I could investigate through my master's paper. Largely through chance I ended up enrolling in a class on Hospital Epidemiology during my MPH year when I was

assigned a presentation on prevention of SSIs. As I read through the CDC guidelines on preventing surgical site infections I came across mupirocin as a potential prophylactic against SSIs. However, the guidelines highlighted the need for randomized clinical trials to address the question and therefore made no recommendations with regards to using intranasal mupirocin preoperatively to reduce SSIs.[8]

Subsequently, when I perused the literature I found several studies and systematic reviews since the above mentioned guidelines were published. Moreover, it was fascinating that the investigations into the role of S. aureus in nasal carriers and nosocomial infections had begun in the 1950s. During my surgical rotations on upper gastrointestinal, plastic or thoracic surgery I had never seen or heard of mupirocin being used as prophylactic. As I further searched the literature I noticed that most of the literature were in cardiac and orthopedic surgical patients and recent systematic reviews on the topic seemed to conclude that intranasal mupirocin as a prophylactic was beneficial in these patients groups. However, given my interest in general surgery I was curious if the same would apply to other surgical procedures given some of the new studies that had been published since the latest systematic review on the topic.

Several systematic reviews have been done on the topic of use of mupirocin in recuing nosocomial infections including surgical site infections. A systematic review looking at nine RCTs involving 3396 participants concluded that there was a significant reduction in the rate of SSIs associated with mupirocin use in nasal carriers RR = 0.55 95% CI 0.34-0.89. However, they found that this effect disappeared when including only SSIs caused by S. aureus RR = 0.63, 95% CI 0.38-1.04 (van Rijen, 2008). Another systematic review addressing the same issue, however in carrier and non-carriers concluded that the use of preoperative mupirocin in general surgery patients had no effect on the incidence of SSIs. They did not comment on the effect of the intervention on SSIs specifically caused by S. aureus (Kallen, 2005).

Some systematic reviews have excluded non-carriers whereas others have included non-carriers in their systematic reviews. In addition, since the last systematic review was published in 2013 a small, yet relevant number of studies have been published in the area that I believe warrants another comprehensive systematic review in order to address the question of whether mupirocin's intranasal administration reduces surgical site infections (overall and *S. aureus* specific) in non-orthopedic and non-cardiac surgical patients, and if so whether there is evidence for the emergence of mupirocin resistance, compliance rates and adverse reactions.

Should such an approach significantly reduce infection rates without being outweighed by harms as a result of adverse reactions, costs accrued and emergence of resistant strains the benefits to both the patients and healthcare system would be substantial given the current burden surgical site infections place on both.

Methods

Through the systematic review I will assess whether the use of mupirocin or a combination of mupirocin and chlorhexidine reduces the incidence of surgical site infections in non-orthopedic and non-cardiac surgical populations postoperatively.

Eligibility Criteria

I adopted a search strategy that would attempt to identify prospective randomized controlled trials. I excluded all other study designs especially case series, case controls, and studies that used historical controls. I chose to do so as the latter study designs tend to have poor internal validity and therefore would reduce the level of certainty in my conclusions.

The analytic framework in *Figure 5* provides an overview of the systematic review and *Table 4* details the population, interventions, outcomes, and adverse events that guided my literature search and subsequent data synthesis and analysis.

I attempted to identify studies that were done in all ages, and both genders with the exposure defined as all types of surgery excluding cardiac and orthopedic procedures. These procedures were excluded as the use of mupirocin in these patient populations has been suggested to be beneficial in several recent systematic reviews, but not as clearly in the case of other surgical subspecialties.[9-11] I identified studies that used intranasal mupirocin or a combination of mupirocin with chlorhexidine and/or povidone-iodine. I chose this strategy in order to increase the sensitivity of my search as I had noted in my background reading that several studies employed a combination of intranasal mupirocin along with chlorhexidine or povidone iodine applied topically.[9,10,12] I did not set strict inclusion criteria for the duration of mupirocin usage as I had noticed on initial literature review that different studies had varying dosages and frequencies of administrations. Studies employing hospital wide screening strategies, preoperative oral antibiotics or intranasal mupirocin as a part of a larger infection control package were excluded as I considered these to be different from the intervention that I

am interested in leading to possible confounding. I searched for studies that employed either standard treatment or placebo as controls. I excluded studies where the comparison group received either povidone-iodine or chlorhexidine or preoperative oral antibiotics alone or in combination.

I included studies reporting incidence of surgical site infections (overall and S. aureus specific) as my primary outcome. Other outcomes that I considered included the incidence of resistance to mupirocin, patient compliance to the mupirocin regimen, and incidence of adverse events as a result of preoperative prophylaxis. I did not use strict inclusion criteria with regards to definition on SSIs as most studies I had reviewed used the CDC definition with the occasional study not making their criteria clear. This systematic review focused on incidence of surgical site infections in the postoperative setting as the key outcome. I searched databases until May, 2015 and did not limit my start date as reports of the role of S. aureus in postoperative complications date back to the 1950s.[13,14] I included studies that were reporting outcomes during the 30 days postoperatively as the CDC definition of a surgical site infection limits the time to follow up at 30 days postoperatively except in the case of surgeries that use implants when the time period is extended to a year.[15] Lastly, I limited my search to studies with full-text available in English.

I attempted to address the following questions in this systematic review.

1. In patients who are candidates for non-orthopedic and non-cardiac surgical procedures does intranasal mupirocin in the preoperative setting reduce the incidence of surgical site infections (as defined by the CDC) postoperatively when compared with placebo or standard treatment?
2. In patients who are candidates for non-orthopedic and non-cardiac surgical procedures receiving intranasal mupirocin in the preoperative setting what is the incidence of reported resistance to mupirocin when compared with placebo or standard treatment?

3. In patients who are candidates for non-orthopedic and non-cardiac surgical procedures does intranasal mupirocin in the preoperative setting lead to any adverse reactions when compared with placebo or standard treatment?
4. In patients who are candidates for non-orthopedic and non-cardiac surgical procedures what is the patient compliance rate associated with regimens of intranasal mupirocin when compared with placebo?

Data Sources and Searches

I searched MEDLINE and Embase electronic databases for studies published until May 11, 2015 that were published in the English language. I did not set a cut off for the start date as I wanted to include even the earliest articles addressing/related to this topic. Investigations on the role of *S. aureus* in nosocomial infections date back as far as 1959 when Williams et al. in 1959 studies the association between nasal carrier state of S. aureus and the incidence of postoperative complications.[13] I conducted the searches with the assistance of an information technologist familiar with creating search strings for several extensive systematic reviews done by faculty at the University of North Carolina at Chapel Hill.

I included all peer reviewed publications within the search results. There were several search results without abstract that were comments or letters to the editor of various journals. These were included at the title review, and abstract review stage. They were excluded at the full text review stage but relevant points were made not of if it would inform my critical appraisal of the included studies, discussion and conclusions.

I also contacted Glaxo SmithKline (GSK) to identify any unpublished studies that addressed this question and was provided with one study that did not meet the inclusion criteria, but did inform my discussion of the results.

Study Selection

Search results were initially screened through title review to identify articles that were obviously not pertaining to the topic at hand. The inclusion and exclusion criteria were strictly applied during the abstract review stage. I included articles that did not have an abstract at this stage as I had planned on increasing sensitivity during this portion of the search. Article exclusions also occurred at the full text review stage and data abstraction stage but not without review of the full text.

All excluded articles were coded with the following corresponding reasons for exclusion:

1. Not original research
2. Ineligible population
3. Ineligible intervention
4. Ineligible comparator
5. Ineligible study design
6. Review
7. Ineligible outcome

I was able to do this using Microsoft Excel 2013. Using this software further allowed me to tabulate how many articles were excluded for each reason during abstract and full text review stages.

Quality Criteria

Risk of bias assessment was done by me using the critical appraisal template developed by the United States Preventive Services Task Force (*Tables 9-12*). Studies were rated as + to +++ with + being good and +++ being of poor quality with significant risk for bias. The following were incorporated into evaluating for risk of bias – initial comparability of treatment and control arm/s, potential for selection and measurement bias and confounding. These helped inform my assessments of the results' internal and external validity.

Data Abstraction

I reviewed all titles, abstracts, full texts and performed data abstraction. As a lot of the studies did not provide detailed information on the patient population, intervention, and controls in the abstract several studies had to be moved into the full text review stage in order to appropriately apply the inclusion/exclusion criteria.

The following study information was abstracted for all included studies:

1. Author/s
2. Published year
3. Study design
4. Country
5. Potential conflict of interest
6. Study period
7. Type of surgery
8. Treatment arm size
9. Control arm size
10. Type, dosage and frequency of treatment arm intervention
11. Type, dosage and frequency of control arm intervention
12. Definition of SSIs and method of assessment
13. Period of follow up
14. Harms assessment done? (Yes/No)
15. Compliance assessment done? (Yes/No)
16. Screening for colonization? (Yes/No)
17. Culture confirmation of SSI pathogen? (Yes/No)
18. Perioperative care characteristics

The following information was then abstracted for patient characteristics:

1. Mean Age
2. Percentage of Caucasians
3. Percentage of Males
4. Percentage of patients with diabetes mellitus
5. BMI
6. Percentage of smokers (current/former)
7. Percentage of immunosuppressed patients
8. Length of preoperative stay
9. Percentage of patients with cancer (proxy of history of chemotherapy/radiation also accepted)
10. Length of surgery
11. Type of surgery

The following information was collected with regards to primary secondary outcomes

1. Study arm sizes
2. Carriage rate
3. Incidence of SSI
4. Incidence of S. aureus specific SSI
5. Measures of associations reported
6. Harms assessments
7. Compliance assessments
8. Resistance to mupirocin assessments

Data synthesis and Assessment

I synthesized my findings for each of the key questions by summarizing the results in tables in a numerical or narrative format as seen appropriate for the outcome under consideration.

Results

Search results

A total of 162 results were identified across MEDLINE, Embase and searching through references. 51 of these articles were selected for full text review. Of these 4 met all the inclusion criteria and were selected for qualitative analysis (*Figure 4*). Studies were excluded at title review, abstract review and full text review for several reasons as detailed in *Figure 6*. The primary reasons for exclusions during the abstract review stage included: not original research, ineligible population, ineligible intervention and ineligible study design. I excluded the majority of articles during full text review because they were either not original research (comments/response to articles) or because the study was done in an ineligible population (cardiac or orthopedic surgical patients).

Description of studies

All the studies that finally met inclusion criteria were randomized controlled trials (Table 1).[16-19] Only one of the studies was double blinded.[16] While two studies were conducted in the United States, [16,18] the other two were done abroad in Japan[17] and Australia.[19]

As mentioned earlier this systematic review aims to review literature within non-orthopedic and non-cardiac surgical patients. The studies included spanned the following surgical specialties: Mohs micrographic surgery,[19] head and neck,[18] abdominal digestive surgery (excluding colorectal and laparoscopic),[17] and a combination of specialties predominated by non-cardiac surgeries.[16] Most of the studies enrolled around or less than 200 patients in each treatment arm except for one that evaluated a total of 3869 patients.[16] All of the studies used mupirocin ointment in the treatment arm. However, two of the studies detailed using chlorhexidine body washes in addition to intranasal mupirocin ointment. All the studies except for one[17] used a 5 day preoperative regimen. Frequency of dosing varied between studies being anywhere form once daily to three times a day.

All studies except for one[19] used CDC definitions to identify surgical site infections and followed patients for a period of 30 days postoperatively to determine the incidence of surgical site infections. Two studies undertook harms assessment and addressed compliance concerns with such interventions.[16,19] Lastly, three of the studies implemented screening in order to identify carriers of S. aureus.[18,19] The other two studies looked at both carriers and non-carriers and did not perform preoperative screening in order to stratify treatments.[16,17]

Risk of bias in included studies

All four included studies were prospective randomized controlled trials. The studies varied in their potential for risk of bias. Given that randomization was performed the potential for selection bias was minimal in all four included studies. Moreover given that the comparison groups were comparable at baseline this further reduced the likelihood for selection bias. However, the primary concern for all four studies included potential for confounding. The reason for this being that three out of the four studies did not report on several baseline attributes that should have been reported such as diabetes status BMI, smoking, previous surgeries, and other comorbidities. The potential for measurement bias was minimal in all but one study given that they all used standardized definitions for assessing SSIs. One notable source of measurement bias is at the intervention level as compliance was reported in only two out of the four studies included in the systematic review. Due to the above reasons I deemed the potential for bias to be high in one study, low in another and medium in the remaining two studies.

Generalizability

The generalizability of these studies vary significantly. One of the studies report results in dermatological surgery patients. Another study reports results in head and neck surgery patients. The other two report on a combination of surgical patient populations. Also some of the studies did not report on several important baseline characteristics such as BMI, smoking status, length of preoperative stay and presence of diabetes mellitus, and use of

immunosuppressants questioning the generalizability of these studies to the general population. Moreover, two of the four studies were conducted abroad which may limit their generalizability to patient populations in the United States.

Outcomes

Incidence of Surgical Site Infections and S. aureus specific Surgical Site Infections

Only one of the two studies that used both mupirocin and chlorhexidine reported on overall incidence of surgical site infections postoperatively compared to standard treatment.[20] There was no statistically significant reduction when compared to standard treatment. The other study reported on *S. aureus* specific surgical site infection incidence alone which is mentioned below.[20]

One of the two studies that employed mupirocin alone in the treatment arm instead of a combination of mupirocin and chlorhexidine as mentioned above did not report on overall SSI incidence instead reporting S. aureus specific surgical site infection incidence which is reported below.[21] The other study did not report a statistically significant trend of reduction in surgical site infections incidence postoperatively compared to placebo and standard treatment.[16]

Only two of the four studies reported S. aureus specific surgical site infection incidence. One of them used both mupirocin and chlorhexidine in the treatment arm[19] whereas the other used mupirocin alone.[16] Both of these studies did not report a statistically significant reduction compared to placebo or standard treatment.

Adverse Reactions

None of the studies included reported life threatening adverse reactions. However, three of the four studies mentioned adverse reactions of different kinds.[16,18,19] One study limited their reporting on harms to mentioning that the treatment was “safe and well tolerated”.[19] Another study took a similar approach and mentioned that “No patients in the treatment group reported

complications with the decolonization protocol".[18] The largest study included in this systematic review listed similar complication rates in the treatment and placebo arm at 4.8% each. The side effects reported were rhinorrhea and itching at application site. Additionally, the authors note that five patients in the study withdrew secondary to adverse effects such as nasal bleeding, nasal burning, and headache. One of these patients received mupirocin whereas the other four were in the placebo arm.[16]

Resistance to Mupirocin

Only one of the studies provided data on the incidence of mupirocin resistance during their study period.[16] Four of the isolates from the nares of patients were resistant to mupirocin. Three of these isolates were from those in the placebo arm, whereas the other one was from the mupirocin arm.

Patient Compliance

Only one[18] of the four studies provided numerical data on compliance. 2 patients in the treatment group (5%) in this study were excluded due to non-adherence to the treatment regimen. The authors did not clarify the reasons for non-adherence.

Discussion

Systematic Review Findings

Incidence of Surgical Site Infections and S. aureus specific Surgical Site Infections

The latest guidelines on antimicrobial prophylaxis in surgical patients only make recommendations regarding the use preoperative mupirocin in cardiac and orthopedic patients. The authors suggest that there is enough evidence to provide mupirocin decolonization to all candidates for cardiac surgery who are colonized with S. aureus. However, the recommendation is not as strong in the case of orthopedic surgery patients with the guidelines suggesting that there may be some benefit to using preoperative mupirocin decolonization in elective cases.[22,23]

In this systematic review I have found no evidence to support the use of mupirocin to reduce surgical site infections in non-cardiac and non-orthopedic surgical populations. However, this is not to suggest that there is no benefit to be derived from pre-operative decolonization with mupirocin in these patients. Instead, given that there is supporting evidence in cardiothoracic and orthopedic surgical populations it is plausible that such an intervention could be beneficial in other surgical patients too.

My primary concern is that several of the studies included maybe underpowered. Mupirocin has been approved by the FDA for the eradication of nasal decolonization with MRSA in those twelve years and older. All but one of the included studies adopted decolonization strategies in accordance with the prescribing information approved by the FDA (twice a day for five days). Only one study used it for a period of three days, but the authors increased the frequency from two times a day to three times a day. Given that most of the studies adopted a decolonization protocol similar to what the FDA has approved, it is unlikely that the lack of reduction in surgical site infections was due to ineffective decolonization.

Pearl et al. reason that they were not able to detect a reduction in surgical site infections likely due to their low incidence in the study population thus under powering their study. Moreover, they noted some of the surgical site infections were a result of transmission from healthcare workers and/or other patients which wouldn't be prevented by an intranasal mupirocin application.

Much like Pearl et al., Suzuki et al. did not identify any changes in surgical site infections as a result of preoperative decolonization with mupirocin. They suggest that it is possible that the study design they adopted may not address the complexity of surgical site infections in digestive surgery patients. The authors note that many of the surgical site infections they detected were mixed gram negative and gram positive infections. In addition, the study did not attempt to stratify participants based on carrier status. *S. aureus* carrier status has been shown to be a significant risk factor in developing surgical site infections. This could have led to further under powering of the study.

Although Tai et al. claim to find a statistically significant reduction in surgical site infections in nasal carriers, I do not believe that this is the case given that the calculated relative risk contains the null value. Similar to the other three studies included, Shuman et al did not find a statistically significant reduction in surgical site infections either. The authors reason that it is likely due to the underpowered study design. Additionally, just like Suzuki et al. they did not stratify interventions based on *S. aureus* carrier status.

The 2008 NICE (National Institute for Health and Care Excellence) guidelines which were updated in 2014 recommended against using nasal mupirocin for nasal decolonization (even in carriers) citing a lack of sufficient evidence of benefits outweighing harms.[24] A recent update to these guidelines made no further mention of the use of mupirocin.[25] In a set of recommendations released in 2011, Alexander et al. briefly mentioned that mupirocin has been shown to reduce surgical site infections based on a then recent systematic review.[26] However,

this particular review involved cardiac, orthopedic and notably non-surgical patients. Therefore, I do not believe that this recommendation is applicable to the non-cardiac and non-orthopedic surgical populations that my systematic review focuses on.

As the reader may have noted, the theme underlying the four included studies is that of underpowered study designs to detect a plausible reduction in surgical site infections, and/or S. aureus specific surgical site infections. As a result I cannot make recommendations for or against the preoperative use of intranasal mupirocin to reduce surgical site infections. However, it is important to take into account that, Pearl et al. found a statistically significant decrease in overall nosocomial infections which between the treatment and control arms. It is plausible that the correct question to ask going forward would be the effect of preoperative mupirocin decolonization on overall hospital acquired infections rather than surgical site infections alone.

Adverse reactions

The manufacturer of intranasal mupirocin (BACTROBAN) Glaxo Smith Kline (GSK) studied the adverse reactions as part of another study in 105 subjects in which the intranasal mupirocin formulation was applied to the inside of participants' forearm. 2 (2%) reported adverse reactions. These included rash and paresthesia.[27] In the prescribing information provided with intranasal mupirocin GSK lists the following adverse reactions including systemic allergic reactions such as anaphylaxis, urticaria, angioedemal and generalized rash. Other side effects include, eye irritation, local irritation and *C. difficile* associated diarrhea. In foreign clinical trials the most common reaction was rhinitis, taste perversion and pharyngitis. In domestic trials common reactions included headache, rhinitis, pharyngitis, taste perversion, burning/stinging (17%).[7]

Although GSK reports no fetal harm in animal studies, intranasal mupirocin safety in pregnant mothers has not been established. Moreover, its safety has not been determined in

those under twelve. Notably, GSK states that significant systemic absorption has been found in the neonatal and premature populations unlike in adults. This could potentially impede the use of mupirocin in the preoperative setting in many surgical candidates.

In this systematic review, I have not come across any reports of systemic allergic reactions. However the reader should note that one of the four studies do not provide any information and two of the four only provide cursory statements on the matter. The one study to provide quantitative information reports equal incidence of adverse reactions (rhinorrhea and pruritus at the application site) in both treatment arms.

Although there seems to be no trend in severe adverse reactions I could not reach any conclusions due to the paucity of data on this aspect of mupirocin use in three of the four included studies.

Resistance to Mupirocin

The mechanism of resistance development is the production of modified isoleucyl-tRNA synthetase or acquisition of a new isoleucyl t-RNA synthetase through plasmid transfer. Cross resistance to other antibacterial have not been reported yet. In an article discussing resistance in *S. aureus* to mupirocin the authors noted that given detection of *in vitro* resistance it is quite plausible that *in vivo* resistance was to be expected. They concluded by cautioning that "extensive use of mupirocin on the skin without proven clinical indication is unwise." However it should be noted that these recommendation were primarily based on topical rather than intranasal use of mupirocin.[28]

A recent review on the topic of resistance in *S. aureus* to mupirocin does not specifically make recommendations with regards to use of intranasal mupirocin. However they suggest that unrestricted use of the antibiotic has been associated with increased incidents of resistance.

They suggest active surveillance in patient populations should mupirocin decolonization be adopted on a larger scale.[29]

Only one among the four studies included in this systematic review provided quantitative reports on the incidents of resistance. The other three studies acknowledge that the use of mupirocin could potentially result in resistant strains. However, they minimize the concern by citing studies that point out that resistance does not emerge unless the antibiotic is used indiscriminately. They conclude that using mupirocin in the preoperative setting is unlikely to cause resistance. Although this may very well be the case I believe that it would be advisable to incorporate active surveillance for resistance against mupirocin in future studies and interventions.

Patient Compliance

One of the primary concerns regarding the studies I have included with regards to internal and external validity is the degree of patient compliance with the decolonization regimen. Only one of the four studies reported qualitative and/or quantitative data on compliance. The other studies implied that the patients were adherent through generalized statements about there being no adverse reactions to the treatment regimens.

Therefore it is difficult to for me to draw any conclusions regarding the rate of patient compliance from the studies that I have included. This is however an important parameter to be included in future studies as this will in turn affect both the internal and external validity of the results.

Limitations of the Review

I acknowledge that there are several limitations to this systematic review. One of them being that study selection was not done through dual review. Lack of dual review could have possibly resulted in inclusion/exclusion of articles erroneously for a variety of reasons. However

I hope that my meticulous approach utilizing a high sensitivity strategy during title and abstract review has minimized this as much as possible. I have not been able to conduct a search of the references of articles to identify any studies that may not have been identified in the initial search. This could have reduced the sensitivity of the search for studies. Additionally, the populations such as dermatological surgery, head and neck surgery, cardiac surgery, gynecologic surgery, and general surgery. This limits the external validity of the study conclusions further limiting my ability to extrapolate from their conclusions. However, I had to adopt this approach as the number of studies in non-orthopedic and non-surgical populations are limited.

Additionally, I had not anticipated that some of the studies would use both mupirocin and chlorhexidine in the treatment arm. I share the reader's concern that this is a different intervention compared to mupirocin alone. However, given the limited number of studies in this area I decided to approach the outcomes from both treatment strategies in order to identify any potential differences in outcomes.

Implications for Practice

Given the limited external validity of the studies that I have included in my systematic review it is difficult to come to a conclusion regarding the external application of the results of the included studies. The studies vary widely in the patient population enrolled. Moreover patients are from very different countries with two studies enrolling patients in the United States, another one in Japan and the last one in Australia. It is important to take into consideration that the health care systems, medical personnel and infection control practices vary between these countries and could account for differences in results should such practices be standardized universally. Moreover several of these studies did not report on key baseline attributes especially comorbidities which make it difficult to translate the results of this systematic review and of the included studies to patients.

Although *S. aureus* has been recognized as a leading cause of surgical site infections it is quite possible that between subspecialties leading cause of surgical site infections might vary. I believe that studies need to be conducted in specific surgical populations that share common causative organisms and mechanisms of infections. An important example of the observation by Suzuki et al. that mixed gram negative and positive infections were the predominant surgical site infections seen in their study of patients undergoing digestive surgery. Therefore at this point I'm not able to recommend the use of mupirocin or against the use of mupirocin in the preoperative setting in non-cardiac and non-orthopedic surgical populations in order to reduce surgical site infections.

Implications for Research

Given the heterogeneous nature of the populations and the interventions employed in these studies it is essential that research be conducted in specific subspecialties rather than in patient populations from several specialties unless upon stratification they are adequately powered. It is important that these studies be adequately power to avoid findings that may be clinically meaningful but cannot be adopted due to lack of statistical significance as seen in the studies included in this systematic review.

Moreover future studies need to take into account several confounding factors including body mass index, diabetes mellitus status, carrier status, immunosuppressive status, cancer status, age, smoking status in order to avoid some of the confounding concerns seen in several studies included in the systematic review. Such an approach is essential because the use of mupirocin has been concluded to be potentially beneficial in cardiac an orthopedic surgical populations and should patients benefit from such a simple intervention with very few adverse reactions it would be both lifesaving and cost-saving in the long run. As of now there aren't enough studies to provide robust evidence on whether such an intervention would be helpful in

surgical populations outside of cardiac and orthopedic populations as shown in my systematic review.

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Figures

Figure 4: Disposition of Articles

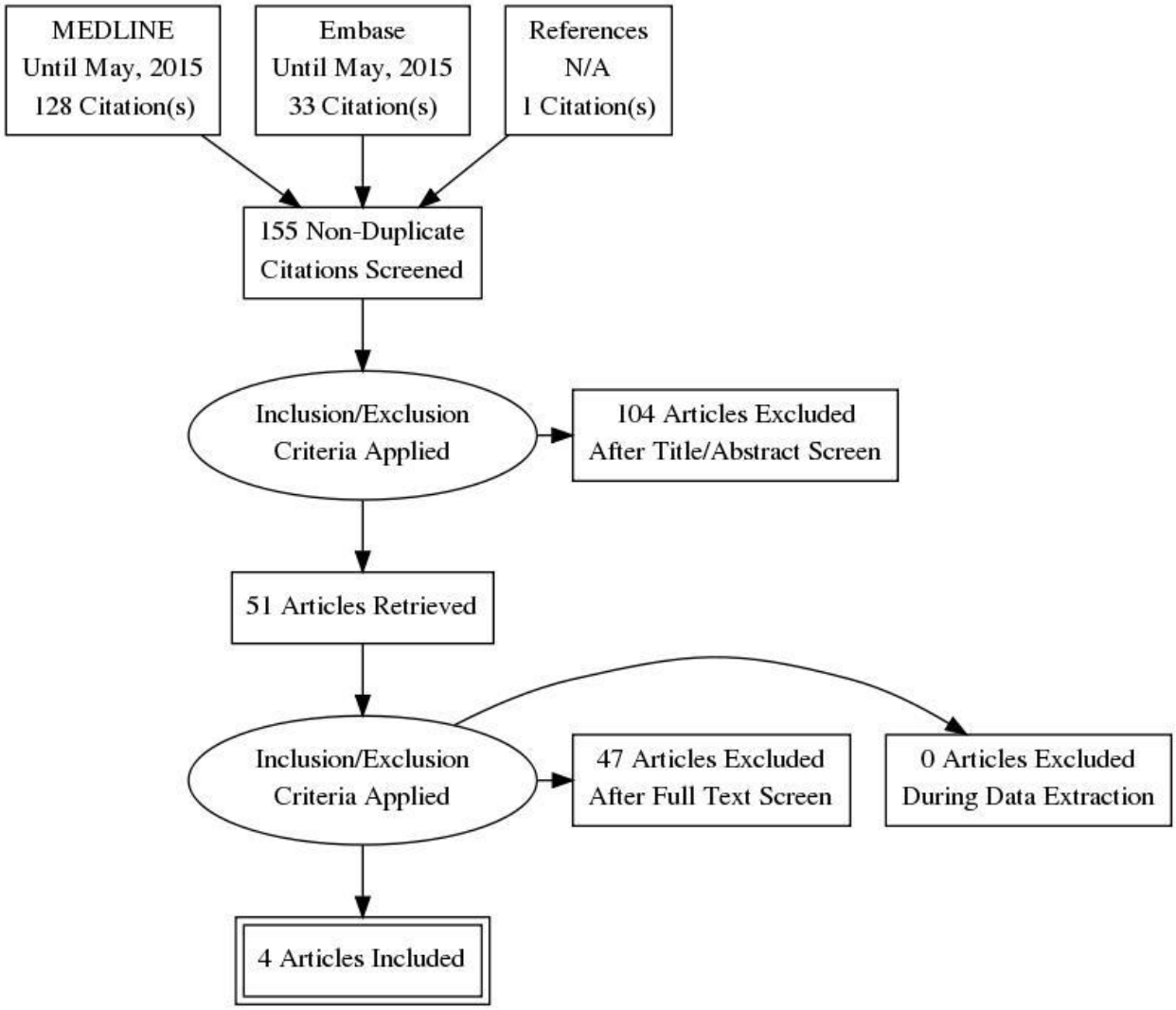


Figure 5: Analytic Framework

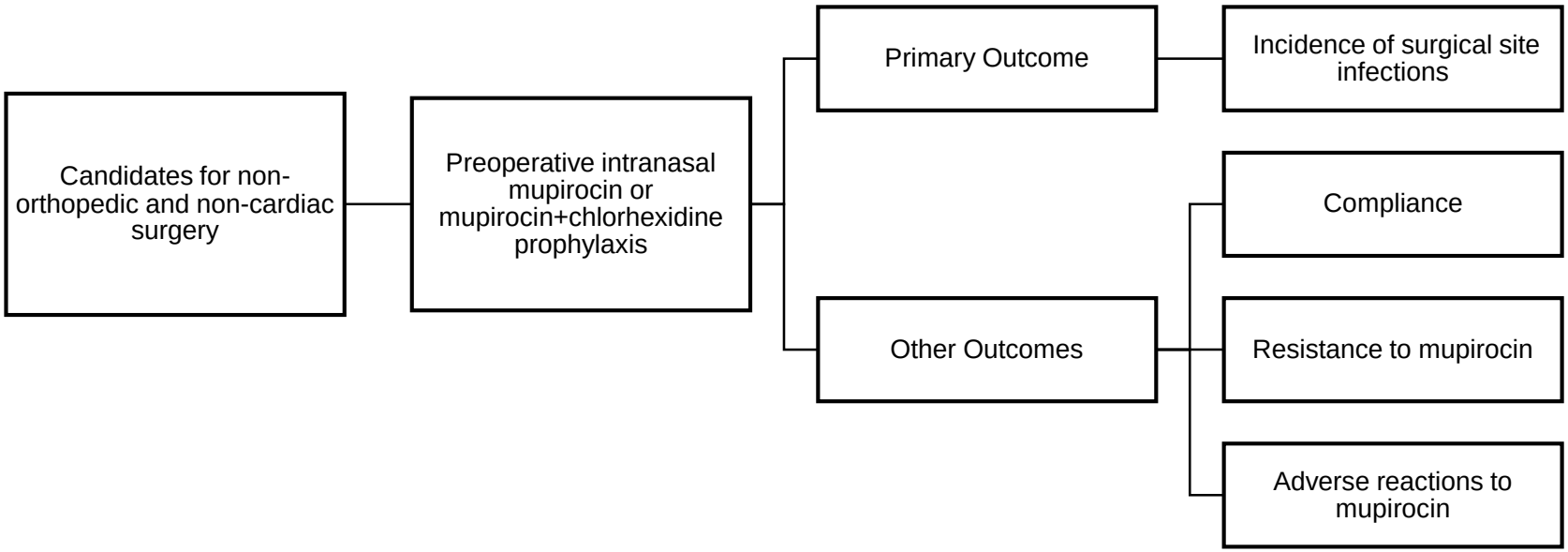
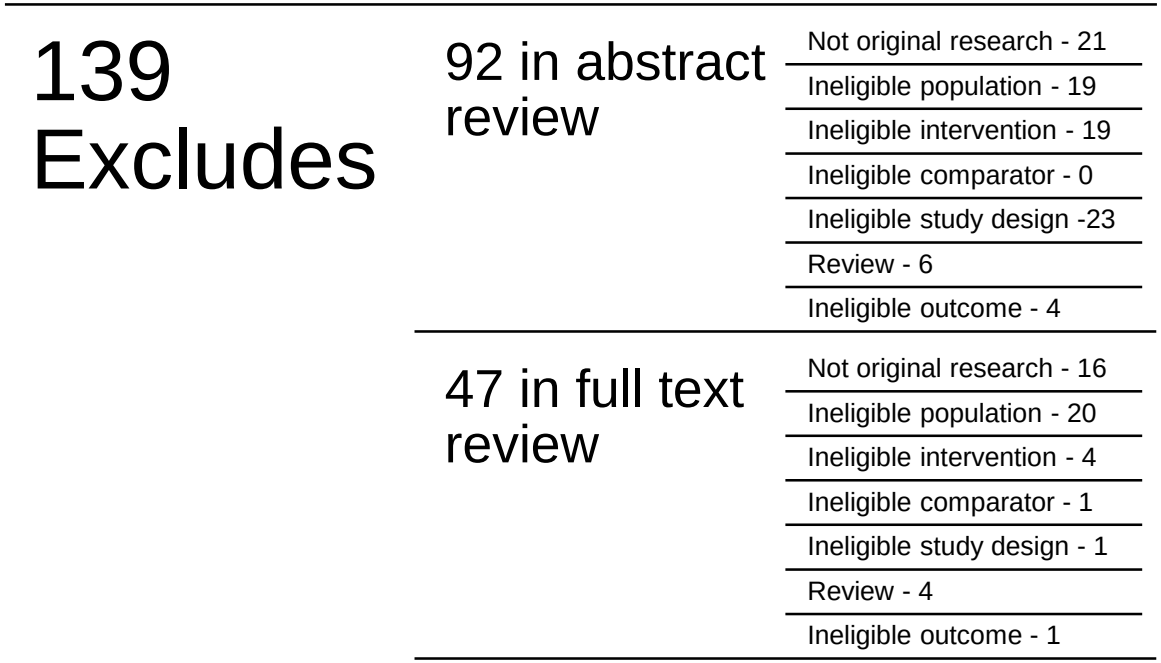


Figure 6: Article Exclusions



Tables

Table 3: Search Strategies

Searches last updated on: 05/11/2015

Database	Search String	Results
MEDLINE	*(("surgical wound infection"[MeSH Terms] OR ("surgical"[All Fields] AND "wound"[All Fields] AND "infection"[All Fields]) OR "surgical wound infection"[All Fields] OR ("surgical"[All Fields] AND "site"[All Fields] AND "infection"[All Fields]) OR "surgical site infection"[All Fields] OR (("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgical"[All Fields]) AND site[All Fields] AND ("infection"[MeSH Terms] OR "infection"[All Fields] OR "infections"[All Fields]))) AND (("administration"[All Fields] AND "intranasal"[All Fields]) OR "intranasal administration"[All Fields] OR ("intranasal"[All Fields] AND "administration"[All Fields]) OR "nose"[MeSH Terms] OR "nose"[All Fields] OR "nasal"[All Fields])) AND ("mupirocin"[MeSH Terms] OR "mupirocin"[All Fields] OR "chlorhexidine"[MeSH Terms] OR "chlorhexidine"[All Fields] OR "povidone-iodine"[MeSH Terms] OR "povidone-iodine"[All Fields] OR ("povidone"[All Fields] AND "iodine"[All Fields]) OR "povidone iodine"[All Fields]) AND English[lang]*	128
Embase	*'povidone iodine'/exp OR 'chlorhexidine'/exp OR 'pseudomonic acid'/exp OR mupirocin AND ('intranasal drug administration'/exp OR nasal AND administration OR nose OR nasal OR intranasal) AND drug AND administration AND ('surgical infection'/exp OR 'surgical site infections') AND [embase]/lim NOT [medline]/lim AND [english]/lim*	33

Table 4: Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	• Patients of all ages and genders undergoing all types of surgery excluding cardiac and orthopedic procedures.	• Cardiac surgery • Orthopedic surgery
Intervention	• Intranasal mupirocin application alone or in combination with chlorhexidine body wash.	• Studies combining intranasal mupirocin with other interventions such as screening and/or infection control measures. • Preoperative oral antibiotics
Comparator	• None or placebo	• Use of povidone-iodine or chlorhexidine alone in any delivery mechanism. • Preoperative oral antibiotics
Outcomes	• Incidence of SSI • Incidence of S. aureus specific SSI • Resistance to mupirocin • Compliance • Adverse events	N/A
Time Period of Included Literature	• Until 05/2015	N/A
Outcome Timing	• Within 30 days postoperatively	N/A
Study Designs	• Prospective randomized controlled trials	• Case series • Case controls
Language	• English	• Non-English

Table 5: Study Characteristics

	Tai et al. 2013	Shuman et al. 2012	Suzuki et al. 2003	Perl et al. 2002
Study Design	Randomized control trial	Randomized control trial	Randomized control trial	Randomized, double blind, placebo controlled trial
Country	Australia	United States	Japan	United States
Potential Conflict of Interest	No information provided	One medication donated by a biomedical company but authors declare no role on part of company in study.	No information provided	Study supported by research grant from GlaxoSmithKline (GSK). Some authors including first author have serves as paid lecturers for GSK.
Study period	April 1, 2011 – October 31, 2011	NR	June 1998 - December 2000	April 1995 - December 1998
Type of Surgery	Mohs Micrographic Surgery (MMS)	Head and neck	Abdominal digestive surgery excluding colorectal and laparoscopic surgery	Elective and non-emergency cardiothoracic, general, oncologic, gynecologic, and neurologic surgical procedures.
Treatment Arm Sample Size	65 (swab positive)	42	193	2012 (1933 evaluated)
Control Arm Sample Size	65 (swab positive)	42	202	2018 (1931 evaluated)
Additional control arm sample size	59 (Swab negative)	N/A	N/A	N/A
Treatment	Twice daily intranasal mupirocin 2% ointment and daily face and full body wash with chlorhexidine gluconate 4% aqueous solution for 5 days pre-operatively	Mupirocin 2% ointment applied intranasally once daily and 2% chlorhexidine gluconate baths once daily during the 5 days leading up to surgery	30 mg mupirocin calcium hydrate ointment via Q-tip swab to each nostril three times a day on each of the 3 days prior to operation	Cotton swab by heath care workers or patients with mupirocin twice daily for up to 5 days before procedure

	Tai et al. 2013	Shuman et al. 2012	Suzuki et al. 2003	Perl et al. 2002
Control	No treatment	No treatment (MSSA and –ve cultures)	No intranasal mupirocin given	Cotton swab by health care workers or patients with placebo twice daily for up to 5 days before procedure
Assessment of SSI	Not detailed	CDC definitions; review of medical records	Blinded assessors using CDC definitions	CDC definitions; three blinded physicians reviewed records to ensure appropriate diagnosis of SSIs.
Period of follow up	Not detailed. Provider dependent.	30 days	30 days	30 days on average. Study personnel monitored inpatients, and reviewed medical records. Also, telephone discharged patients weekly. Patients instructed to contact study personnel if signs of infection seen.
Harms assessment	Yes	Yes; patient self-report	No	Yes; study personnel interviewed patients.
Compliance assessment	Yes	No	No	Yes; study personnel reviewed medical cards and diary cards listing dates and times of intervention administration.
Screening for colonization	Yes; swab and culture	Yes; swab and culture	No	Yes; swab and culture
Culture confirmation of SSI pathogen	Yes	“Obtained when appropriate”	Yes	Yes

	Tai et al. 2013	Shuman et al. 2012	Suzuki et al. 2003	Perl et al. 2002
Perioperative care	No other antimicrobial prophylaxis	Non-carriers and those with MSSA received routine preoperative antimicrobial prophylaxis. Those colonized with MRSA received additional perioperative antimicrobial prophylaxis directed against MRSA.	Detailed in both treatment and control arms; comparable	Standard prophylactic regimens used when appropriate. Cardiac surgery candidates had chlorhexidine body wash the night before and the morning of the procedure.

Table 6: Patient Characteristics

		Mean Age (years)	White/Caucasian (no., %)	Male (no., %)	Diabetes Mellitus (no., %)	BMI +/- SD	Smokers (Current and/or previous) (no., %)	Immunosuppression (no., %)	Preoperative stay (days)	Cancer (no., %)	Length of surgery (mins)	Type of Surgery
Tai et al., 2013	Total	65	NR	59%	NR	NR	NR	NR	NR	NR	NR	NR
	Non-carrier	65	NR	57%	NR	NR	NR	NR	NR	NR	NR	NR
	Carrier Control	67	NR	65%	NR	NR	NR	NR	NR	NR	NR	NR
	Carrier Tx	64	NR	65%	NR	NR	NR	NR	NR	NR	NR	NR
Shuman et al., 2012	Total	58.14	NR	48 (57%)	10 (12%)	NR	49 (58%)	NR	NR	Chemo 10 (12%) Radiation 19 (23%)	314	NR
	Carrier Control	59.76	NR	25 (60%)	5 (12%)	NR	29 (69%)	NR	NR	Chemo 6 (14%) Radiation 11 (26%)	323	NR
	Carrier Tx	56.52	NR	23 (55%)	5 (12%)	NR	20 (48%)	NR	NR	Chemo 4 (10%) Radiation 8 (19%)	304	NR
Suzuki et al. 2003	Mupirocin	63	NR	127 (66%)	34 (18%)	NR	NR	NR	NR	NR	NR	NR
	Control	52	NR	135 (67%)	42 (21%)	NR	NR	NR	NR	NR	NR	NR
Perl et al., 2002	Total Tx	53.8 +/- 16.3	1873 (96.9 %)	979 (50.6 %)	307 (15.9 %)	28.9 +/- 7.8	583 (30.2%)	198 (10.2 %)	0 d 1152 (59.8%) 1 d 420 (21.8%) 2-7 d 246 (12.8%)	376 (19.5%)	230	General surgery 1206 (62.4) Neurosurgery 364 (18.8) Cardiothoracic 363 (18.8)

		Mean Age (years)	White/Caucasian (no., %)	Male (no., %)	Diabetes Mellitus (no., %)	BMI +/- SD	Smokers (Current and/or previous) (no., %)	Immunosuppression (no., %)	Preoperative stay (days)		Cancer (no., %)	Length of surgery (mins)	Type of Surgery	
									>/= 8d	109 (5.7%)				
	Total Control	54.2 +/- 16.5	1859 (96.3 %)	1016 (52.6 %)	322 (16.7 %)	29.0 +/- 7.9	568(29.4%)	208 (10.8 %)	0 d	1159 (60.1%)	378 (19.6%)	230	General surgery	1202 (62.2)
									1 d	412 (21.4%)			Neurosurgery	368 (19.1)
									2-7 d	237 (12.3%)			Cardiothoracic	361 (18.7)
									>/= 8d	121 (6.3%)				
	Carrier Tx	50.7 +/- 16.1	432 (97.3 %)	233 (52.5 %)	65 (14.7 %)	29.6 +/- 8.5	117 (26.4%)	43 (9.7%)	0 d	263 (59.2%)	83 (18.7%)	226	General surgery	282 (63.5)
									1 d	107 (24.1%)			Neurosurgery	77 (17.3)
									2-7 d	56 (12.6%)			Cardiothoracic	85 (19.1)
									>/= 8d	18 (4.1%)				
	Carrier control	52.0 +/- 17.4	430 (96.2 %)	246 (55%)	71 (15.9 %)	29.9 +/- 8.8	121 (27.1%)	42 (9.4%)	0 d	264 (59.2%)	78 (17.4%)	231	General surgery	272 (60.8)
									1 d	102 (22.9%)			Neurosurgery	95 (21.3)
									2-7 d	64 (14.3%)			Cardiothoracic	80 (17.9)
									>/= 8d	16 (3.6%)				

Table 7: Primary Outcome

	Study Arms	Participants	Carriage Rate (number/percentage)	SSI incidence (number/percentage)	S. aureus specific SSI incidence	Measure of Association
Mupirocin and Chlorhexidine						
Tai et al. 2013	Intentionally empty	738	203 (38%)	32 (4%)	30 (4%)	• **RR = 0.3 (0.1-1.0) P=0.05 (treated carriers vs. untreated carriers)** • RR b/w treated carriers and non-carriers was not statistically significant
	Carrier Tx	102	N/A	4 (4%)	4 (4%)	N/A
	Carrier Control	101	N/A	11 (11%)	11 (11%)	N/A
	Non-carriers	535	N/A	17 (3%)	17 (3%)	N/A
Shuman et al. 2012	Intentionally empty	84	26 (31%)	17% (calculated)	Not reported	• **SSI incidence overall in experimental vs control OR = 0.338 95% CI (0.096-1.177); P=0.079** • S. aureus carriers vs non-carriers overall OR = 0.64; 95% CI = 0.12-19.46; P=0.74 • **Experimental vs control overall in carriers OR = 1.54; 95% CI = 0.12-19.46; P = 0.74**
	Experimental (Carriers and non-carriers)	42	N/A	4 (10)	Not reported	N/A
	Control (Carriers and non-carriers)	42	N/A	10 (24)	Not reported	N/A

Mupirocin Only						
Suzuki et al. 2003	Intentionally empty	395	N/A	50 (13%) calculated	Intentionally empty	
	Mupirocin (carriers and non-carriers)	193	Intentionally empty	28 (14.5)	Not reported	Intentionally empty
	Control (carriers and non-carriers)	202	Intentionally empty	22 (10.9) 14.5 vs 10.94%	Not reported	Intentionally empty
Perl et al. 2002		*3864*	891 (23%) calculated	316 (8.2)	Intentionally empty	• S. aureus OR = 4.5 carrier placebo vs non-carrier placebo; 95% CI = 2.47-8.21; P<0.0001
	Total Tx	1933	447 (23%)	152 (7.9)	43 (2.3)	
	Total Control	1931	444 (23%)	164 (8.5)	46 (2.4)	
	Carrier Tx	444	Intentionally empty	44 (9.9)	16 (3.7)	
	Carrier control	447	Intentionally empty	52 (11.6)	26 (5.9)	
	Non-carrier Tx	1489	Intentionally empty	108 (7.3)	27 (1.8)	
	Non-carrier control	1484	Intentionally empty	112 (7.5)	20 (1.4)	

Table 8: Other Outcomes

	Harms	**Compliance**	**Resistance**
Tai et al. 2013	"Safe and well tolerated." Also, conducted testing prior to study on 786 patients to assess adverse reactions and no contact dermatitis or ocular irritation was noted.	Patient reported	NR
Shuman et al. 2012	"No patients in the treatment group reported any complications with the decolonization protocol."	2 (5) excluded due to non-adherence in both treatment and control arm	NR
Suzuki et al. 2003	NR	NR	NR
Perl et al. 2002	Among 4040 patients randomized 97 of the 2012 in the treatment arm (4.8%) and 96 of the 2018 in the placebo group reported side effects of rhinorrhea and itching at application site. Five patients withdrew because of adverse effects of nasal bleeding, nasal burning and headache. Amongst these one received mupirocin and four received placebo.	NR	Only four isolates resistant to mupirocin (three from placebo arm; 1 from mupirocin arm)

Table 9: Critical Appraisal of Perl et al. 2002

Citation (JAMA style)	• Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. N Engl J Med. 2002; 346(24):1871-7.
Study Question and Research Design	• Does preoperative intranasal application of mupirocin decrease the rate of S. aureus infections at surgical sites and S. aureus nosocomial infections? • Randomized double blind placebo-controlled trial
Source Population	• Patients undergoing elective and nonemergency cardiothoracic, general, oncologic, gynecologic and neurologic surgical procedures at the University of Iowa Hospitals and Clinics and the Veteran Affairs Medical Center in Iowa City between April 1995 and December 1998.
Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc)	• Exclusion criteria – allergy to mupirocin or glycerin ester, pregnant or breast feeding, participating in another clinical trial, history of S. aureus infection in previous month, documented disruption of nasal and facial bones, and insertion of permanent central catheters alone. ○ 166 excluded because of not undergoing an eligible operation (49 in mupirocin group and 48 in placebo group), received no study medication (22 and 26 respectively), or met both exclusion criteria (8 and 13 respectively). • Mostly older White individuals who are overweight and with median of 5 comorbid conditions. Majority of patients had a duration of preoperative stay of 1 day or less.
Initial Comparability of groups (ie, randomization or group composition; concealment of allocation)	• Very comparable groups • Randomization stratified by surgical service • No information on allocation concealment
Drop outs (no endpoint data), adherence, crossovers (attrition, loss to follow up)	• 479 dropouts; 249 (12.4%) in the mupirocin group vs. 209 (10.4%) in the placebo group. 21 patients did not receive study drug. • Swabs on SSIs only performed on 111/152 and 127/164 of mupirocin and placebo arm patients respectively. Reason not given.
Potential for selection bias (+ to +++) and explain	• + • Randomization should minimize this; however it was stratified by service making the likelihood higher than it would have been otherwise. Also, allocation concealment is not reported on in the paper.
Measurement of exposure, intervention, potential confounders, and outcomes; reliability and validity	• Nasal swabs and cultures performed to assess carrier status • Swabs and cultures performed to confirm S. aureus infection of wound • Blinded assessment of SSI

of measurement; how performed, blinding	• CDC definitions employed for SSI • Blinded assessment of compliance
Potential for measurement bias (+ to +++)	• +
Potential confounders (name and describe how each was controlled for)	• Several confounders (age, comorbid illnesses and length of preoperative stay) controlled for through randomization • Not all surgical sites were swabbed and cultured
Potential for confounding (+ to +++)	• +
Analysis (intention to treat or other adjustment)	• Intention to treat analysis
Results: magnitude and direction (point estimate; random error or precision (confidence interval); statistical significance	• Preoperative and postoperative nasal carriage rates virtually unchanged in placebo recipients. • S. aureus eliminated in 83.4% of patients receiving mupirocin whereas in only 27.4% of patients receiving placebo (P<0.001) • In non-carriers 5.9% of placebo recipients had S. aureus in their nares postoperatively whereas only 1.0% of those who got mupirocin did. • 438 (11.3%) patients had nosocomial infections. 218 (11.3%) were in the mupirocin group and 220 (11.4%) were in the placebo group. • SSIs were found in 152 (7.9%) of the mupirocin and 164 (8.5%) in the placebo group. • S. aureus SSIs were found in 43 (2.3%) of the mupirocin and 46 (2.4%) in the placebo group. This is after excluding the patients whose surgical sites were not cultured. • Risk of S. aureus nosocomial infection in nasal carriers treated with mupirocin vs placebo was OR = 0.49 95% CI 0.25-0.92; P=0.02 • Odds of SSIs amongst placebo recipients in carriers vs non-carriers was 4.5 95% CI 2.47-8.21 P<0.001
Overall judgment of internal validity (good, fair, poor)	• Good
External validity: applicability to other populations	• Applicable to the population seen at a tertiary medical center, but may not necessarily translate to ambulatory procedures. Special care should be taken when extrapolating results to specialties that were not represented in this study such as orthopedics, dermatologic surgery and head and neck surgery.
Risk of bias	• +

Table 10: Critical Appraisal of Suzuki et al. 2003

Citation (JAMA style)	Suzuki Y, Kamigaki T, Fujino Y, Tominaga M, Ku Y, Kuroda Y. Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery. Br J Surg. 2003;90(9):1072-5.
Study Question and Research Design	• Does intranasal mupirocin reduce postoperative sepsis rates, including wound infection after digestive surgery compared to the control group receiving no treatment? • Randomized control trial
Source Population	• Patients undergoing “abdominal digestive surgery” at Kobe University Hospital, Japan between June 1998 and December 2000
Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc)	• Older males, with comorbidities of diabetes and liver cirrhosis
Initial Comparability of groups (ie, randomization or group composition; concealment of allocation)	• Comparable with regards to prevalence of diabetes, liver cirrhosis, age and gender distribution.
Drop outs (no endpoint data), adherence, crossovers (attrition, loss to follow up)	• No information provided on dropouts or adherence
Potential for selection bias (+ to +++) and explain	• + • Randomization minimizes chances, however, no mention of use of allocation concealment
Measurement of exposure, intervention, potential confounders, and outcomes; reliability and validity of measurement; how performed, blinding	• No swabs or cultures done preoperatively to assess carrier status • Mupirocin calcium hydrat ointment 30 mg administered using Q-tip swab to each nostril three time a day on each day of the 3 days before the operation. • Control group received no treatment. • SSI diagnosed based on CDC definitions by a team of digestive surgeons and radiologists who were blinded.
Potential for measurement bias (+ to +++)	• + • Unlikely, but possible given minimal information on adherence or compliance to mupirocin regimen.

Potential confounders (name and describe how each was controlled for)	• Prevalence of diabetes and liver cirrhosis in patients accounted for • Other co-morbidities not mentioned • BMI not reported for treatment and control arms
Potential for confounding (+ to +++)	• ++
Analysis (intention to treat or other adjustment)	• No information provided
Results: magnitude and direction (point estimate; random error or precision (confidence interval); statistical significance	• 28 SSI in mupirocin group and 22 in control group with no statistically significant difference between them. • Most SSI were caused by gram negative organisms • 10 SSIs with gram positive organisms in mupirocin and 11 in control group. Of these, 12 were concomitant infections with gram positive and gram negative organisms • Gram positive bacterial alone in 4 (2.1%) of mupirocin and 5 (2.2%) of control arm
Overall judgment of internal validity (good, fair, poor)	• Fair • Many confounders not taken into account, minimal measurement bias or selection bias.
External validity: applicability to other populations	• Findings could be generalizable to inpatients undergoing “abdominal and digestive surgery.” However, given that carrier status was not determined preoperatively conclusions must be drawn with caution.
Risk of bias	• ++

Table 11: Critical Appraisal of Shuman et al. 2012

Citation (JAMA style)	Shuman AG, Shuman EK, Hauff SJ, et al. Preoperative topical antimicrobial decolonization in head and neck surgery. Laryngoscope. 2012;122(11):2454-60.
Study Question and Research Design	• Randomized controlled trial • Efficacy of preoperative topical decolonization with mupirocin and chlorhexidine in reducing SSIs regardless of preoperative decolonization status • Determine proportion of patients colonized with MSSA or MRSA preoperatively • Independent predictors of SSIs in patients undergoing head and neck surgery
Source Population	• Patients attending preoperative otolaryngology clinic prior to elective head and neck surgery requiring admission to the hospital postoperatively.
Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc)	• Mostly older male patients with a current or former history of smoking and prior history of surgery. • Exclusion criteria included patients undergoing ambulatory procedures known hypersensitivity to either mupirocin or chlorhexidine, immunosuppression due to underlying illness or medications and a documented preoperative infection involving the surgical field.
Initial Comparability of groups (ie, randomization or group composition; concealment of allocation)	• Difference among experimental and control group included higher number of non-smokers and S. aureus carriers, lower prevalence of history of prior radiation in the experimental group. • Groups comparable otherwise in terms of age, prior history of chemotherapy, prior history of surgery and history of diabetes.
Drop outs (no endpoint data), adherence, crossovers (attrition, loss to follow up)	• Two patients in each group excluded due to non-adherence to study protocol • Two patients (one in each group) died within 30 days of surgery due to non-SSI related complications and were followed up until then. They were included in the analysis. • 84 of 88 patients in final analysis
Potential for selection bias (+ to +++) and explain	• Unlikely given randomization and good comparability of experimental and control groups at baseline.
Measurement of exposure, intervention, potential confounders, and outcomes; reliability and validity of measurement; how performed, blinding	• Study participants underwent elective head and neck surgery • Preoperative decolonization with mupirocin 2% ointment applied intranasally each day for 5 days leading up to the surgery and 2% chlorhexidine gluconate solution • Control group did not undergo topical decolonization • SSIs assessed based on CDC definitions during a 30 day postoperative follow up period by review of medical records for all patients enrolled in the study.

	• Wound cultures obtained when appropriate
Potential for measurement bias (+ to +++)	• ++ • Measurement bias unlikely at exposure or intervention but possible at outcome as no information given regarding blinding of reviewers of medical records.
Potential confounders (name and describe how each was controlled for)	• Several confounders matches at baseline including history of diabetes, tobacco use, age, and S. aureus carrier status. • BMI not included in baseline characteristics
Potential for confounding (+ to +++)	• +
Analysis (intention to treat or other adjustment)	• Uncertain
Results: magnitude and direction (point estimate; random error or precision (confidence interval); statistical significance	• 10 (24%) SSIs in control group vs. 4 (10%) in experimental group. However, not statistically significant. OR = 0.338; 95% CI 0.096-1.177; P=0.079 • NNT = 7 • 26 (31%) of all participants were carriers of S. aureus. ○ 20 (24%) carried MSSA and 6 (7%) carried MRSA) • S. aureus carrier status not associated w/ increased risk of SSIs. OR = 0.64; 95% CI 0.15-2.48; P=0.49 • Carriers who underwent decolonization did not derive significant benefit from it compared to carriers in the control group. OR = 1.54; 95% CI 1.08-52.26; P=0.04. • Independent risk factors for SSIs included higher ASA Physical Status classification system score, more operative blood loss, and need for operative takeback. • Statistically non-significant trend seen in those undergoing clean-contaminated surgery, with prior history of radiation and/or chemotherapy.
Overall judgment of internal validity (good, fair, poor)	• Fair • Potential for measurement bias, but minimal potential for confounding or selection bias.
External validity: applicability to other populations	• Results may be extrapolated to other elective ENT procedures. However, care should be taken when applying results to any other surgical procedures.
Risk of bias	• +

Table 12: Critical Appraisal of Tai et al. 2013

Citation (JAMA style)	• Tai YJ, Borchard KL, Gunson TH, Smith HR, Vinciullo C. Nasal carriage of Staphylococcus aureus in patients undergoing Mohs micrographic surgery is an important risk factor for postoperative surgical site infection: a prospective randomized study. Australas J Dermatol. 2013;54(2):109-14.
Study Question and Research Design	• Is there a difference in infection rates between nasal carriers and non-carriers of S. aureus after MMS? • Does decolonization with mupirocin ointment and chlorhexidine wash reduce infection rates in nasal carriers? • Prospective randomized non-blinded controlled study
Source Population	• Patients presenting for assessment for MMS between April 1 and October 31, 2011 at private ambulatory day surgical facility in Perth, Australia.
Study Population (descriptive: demographics, eligibility criteria) and how chosen (volunteers, recruitment, tertiary care clinics, population-based, etc)	• Mostly older male patients requiring surgery on the ear nose, and cheek with primarily skin flap used for repair. • Exclusion criteria – already on systemic antibiotics, needing reconstructive surgery elsewhere
Initial Comparability of groups (ie, randomization or group composition; concealment of allocation)	• Carriers were randomized (method not mentioned) • No mention regarding concealment of allocation or blinding • Fairly comparable. However, nasal carriers who underwent decolonization had less skin flap repairs, and less direct closures compared to those who did not undergo decolonization. Also, the former had less operative sites on the nose.
Drop outs (no endpoint data), adherence, crossovers (attrition, loss to follow up)	• 49 dropouts due to “administrative error, need for pre-operative or postoperative oral antibiotics for non-dermatological reasons, patients’ refusal to participate m the study, difficulties in obtaining a preoperative swab and difficulties in contacting patients for decolonization therapy.” • No information on drop outs to assess comparability
Potential for selection bias (+ to +++) and explain	• ++ • Dropouts increase the likelihood even though groups were comparable at randomization.
Measurement of exposure, intervention, potential confounders, and outcomes; reliability and validity of measurement; how performed, blinding	• Swabs and cultures done to assess carrier status • Mupirocin and chlorhexidine intervention done only in carriers in the treatment arm

	• "Clinical signs of infection" indicated a wound swab in the postoperative period and SSI was not diagnosed without positive culture results. • No information provided on blinding
Potential for measurement bias (+ to +++)	• + • Unlikely, but possible given that strict criteria were not developed for surveillance postoperatively. Sensitivity depends on provider engagement.
Potential confounders (name and describe how each was controlled for)	• Age, defect size, number of Mohs stages, anatomic location, and repair type were comparable in the groups initially. • Other potential confounders not accounted for include BMI, smoking status, diabetes mellitus and other comorbid health conditions.
Potential for confounding (+ to +++)	• +++
Analysis (intention to treat or other adjustment)	• As treated analysis

Results: magnitude and direction (point estimate; random error or precision (confidence interval); statistical significance	• RR = 0.3 (0.1-1.0) P=0.05 (treated carriers vs. untreated carriers)
	• RR b/w treated carriers and non-carriers was not statistically significant [RR=1.2 (0.4-3.5)]
	• RR = 3.4 (1.6-7.0) P<0.001 (untreated carriers vs non-carriers)
	• NNT
	  ○ 15 carriers receive decolonization to prevent one SSI
	  ○ 53 patients swabbed to prevent one SSI

Overall judgment of internal validity (good, fair, poor)	• Fair • Although there is limited concern for measurement bias the concerns of selection bias and confounding remain.
External validity: applicability to other populations	• The source population is not necessarily representative of other surgical populations in terms of age, comorbid conditions or procedures undergone. Although, this study could inform studies in other surgical fields the results many not necessarily applicable to those populations.
Risk of bias	• +++